PCT/GB 2003 / 0 0 5 5 4 2

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Andrew Cursey

Dated 25 November 2003

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
H
24 DEC 2002
The Patent Office
NEWPORT

28DEC02 E773929-2 D02934
P01/7700 0.00-0230087.9

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

24 DEC 2002

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 100940

2. Patent application number *(The Patent Office will fill in this part)* — 0230087.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 07957251001

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)*

Thomas Miller

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

07822471002

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	24 /
Claim(s)	5 / CF
Abstract	3 /
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date

Authorised Signatory 23/12/2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C Bennett - 01625 230148

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

THERAPEUTIC AGENTS

Field of invention

The present invention relates to certain 4,5 –diarylthiazole-2-carboxamide compounds, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, and to pharmaceutical compositions containing them.

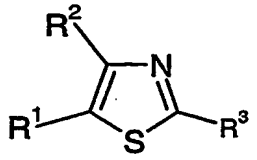
Background of the invention

It is known that certain CB_1 modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB_1 modulators with improved physicochemical properties and/or DMPK (distribution, metabolism and pharmacokinetic) properties and/or pharmacodynamic properties.

Certain *N*-acyl-4,5 –diarylthiazoles-2-alkylamines and *N*-acyl-4,5 –diarylthiazoles-2-carboxamides are reported to have antithrombotic activity in EP388909 and EP 377457. Other such thiazoles are disclosed in British Journal of Pharmacology (2002), 135(3), 782-788;European Journal of Pharmacology (2000), 391(1/2), 49-54 ;Bioorganic & Medicinal Chemistry (1999), 7(8), 1559-1565; WO9420475; WO9420476; Journal of Medicinal Chemistry (1994), 37(8), 1189-99; Journal of Pharmacology (1993), 243(2), 179-84; European Journal of Pharmacology (1993 Oct 19), 243(2), 179-84; and the Journal of Medicinal Chemistry (1994 Apr 15), 37(8), 1189-99. The compounds disclosed in these documents are disclaimed from the compound claims of the present invention.

Description of the invention

The invention relates to compounds of the general formula (I)



I

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one , two or three groups represented by Z;

Z represents a C_{1-6}alkyl group, a C_{1-6}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl , acetyl or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ; and phenyl optionally substituted by one or more of the following: C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, trifluoromethoxy, or halo or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ;

and

R^3 represents a group –X-Y-NR^4R^5 in which

R^4 and R^5 independently represent :

a C_{1-6}alkyl group optionally substituted by a C_{1-6}alkoxy group or trifluoromethoxy;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

a non-aromatic C_{3-15}carbocyclic group which is optionally substituted by a C_{1-3}alkoxyC_{1-3}alkyl group ;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group $-(CH_2)_r(\text{phenyl})_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups or benzyl ;

1-adamantylmethyl;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more. C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-6}alkyl group; a C_{1-6}alkoxy group, trifluoromethoxy or halo or Het represents a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

or R^4 represents H and R^5 is as defined above;

or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

X is CO or SO_2;

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

with the proviso that R^1 and R^2 do not both represent 4-methoxyphenyl and the proviso that when R^1 represents phenyl and R^2 represents phenyl or 4-flouorophenyl, X is CO and Y is absent then the group NR^4R^5 does not represent methyl-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]amino, methylpiperazino, 2-[1-methyl-4-piperidinyl]ethylamino; or [2-

[1-(phenylmethyl)-4-piperidinyl]ethyl]amino.

Further values of R^1, R^2 and R^3 in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one group of compounds of formula I, R^1 represents phenyl optionally substituted by one or two halos, particularly chloro or bromo, or by a C_{1-3}alkoxy group.

In a second group of compounds of formula I, R^1 represents a 2,3-dihydrobenzo[1,4]dioxinyl group optionally substituted by one or more halo.

In a third group of compounds of formula I, R^1 represents phenyl, 4-chlorophenyl, 4-bromophenyl, 4-methoxyphenyl, 2,4 dichlorophenyl or 7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl.

In a fourth group of compounds of formula I, R^2 represents phenyl optionally substituted by one or two halos, particularly chloro or bromo, or by a C_{1-3}alkoxy group.

In a fifth group of compounds of formula I, R^2 represents a 2,3-dihydrobenzo[1,4]dioxinyl group optionally substituted by one or more halo.

In a sixth group of compounds of formula I, R^2 represents phenyl, 4-chlorophenyl, 4-bromophenyl, 4-methoxyphenyl, 2,4 dichlorophenyl or 7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl.

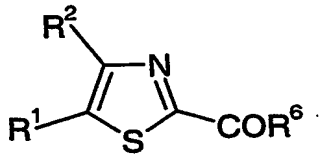
In a seventh group of compounds of formula I, X is CO, Y is absent and R^3 represents a C_{3-7}cycloalkylamino group.

In an eighth group of compounds of formula I, X is CO, Y is absent and R^3 represents pyridylamino.

In an ninth group of compounds of formula I, X is CO, Y is absent and R^3 represents a C_{1-6}alkylamino group wherein the alkyl chain is substituted by one or more of the following: a C_{1-3}alkoxy group, or morpholino.

In a tenth group of compounds of formula I, X is CO, Y is absent and R^3 represents cyclohexylamino, piperidin-1-ylamino, (2-methoxymethylcyclopentyl)amino, pyridin-4-ylamino, (2-ethoxyethyl)amino; or (2-(morpholin-4-yl)ethyl)amino.

One group of compounds of formula I is represented by formula (II)



II

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which

R^1 represents phenyl optionally substituted by one or more of the following: C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, trifluoromethoxy, or halo or two adjacent carbons may be substituted with the group $-O-CH_2-CH_2-O-$;

R^2 represents phenyl optionally substituted by one or more of the following: C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, trifluoromethoxy, or halo or two adjacent carbons may be substituted with the group $-O-CH_2-CH_2-O-$;

and

R^6 represents 1-piperidinylamino, a C_{3-7}cycloalkylamino group which is optionally substituted by a C_{1-3}alkoxyC_{1-3}alkyl group, pyridylamino wherein the pyridyl ring is optionally substituted by one or more of the following: a C_{1-6}alkyl group; a C_{1-6}alkoxy group or trifluoromethoxy; or R^6 represents a C_{1-6}alkylamino group wherein the alkyl chain

is optionally substituted by one or more of the following: a C_{1-6}alkoxy group, trifluoromethoxy or morpholino;
with the proviso that when R^1 represents 4-methoxyphenyl and R^2 represents 4-methoxyphenyl then R^6 does not represent 2-(morpholino)ethyl.

Further values of R^1, R^2 and R^6 in compounds of formula II now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one group of compounds of formula II, R^1 represents phenyl optionally substituted by one or two halos, particularly chloro or bromo, or by a C_{1-3}alkoxy group.

In a second group of compounds of formula II, R^1 represents a 2,3-dihydrobenzo[1,4]dioxinyl group optionally substituted by one or more halo.

In a third group of compounds of formula II, R^1 represents phenyl, 4-chlorophenyl, 4-bromophenyl, 4-methoxyphenyl, 2,4 dichlorophenyl or 7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl.

In a fourth group of compounds of formula II, R^2 represents phenyl optionally substituted by one or two halos, particularly chloro or bromo, or by a C_{1-3}alkoxy group.

In a fifth group of compounds of formula II, R^2 represents a 2,3-dihydrobenzo[1,4]dioxinyl group optionally substituted by one or more halo.

In a sixth group of compounds of formula II, R^2 represents phenyl, 4-chlorophenyl, 4-bromophenyl, 4-methoxyphenyl, 2,4 dichlorophenyl or 7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl.

In a seventh group of compounds of formula II, R^6 represents a C_{3-7}cycloalkylamino group.

In an eighth group of compounds of formula II, R^6 represents pyridylamino.

In an ninth group of compounds of formula II, R^6 represents a C_{1-6}alkylamino group wherein the alkyl chain is substituted by one or more of the following: a C_{1-3}alkoxy group, or morpholino.

In a tenth group of compounds of formula I, R^6 represents cyclohexylamino, piperidin-1-ylamino, (2-methoxymethylcyclopentyl)amino, pyridin-4-ylamino, (2-ethoxyethyl)amino; or (2-(morpholin-4-yl)ethyl)amino.

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid;

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl . Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention are:

4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid cyclohexylamide;
5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid cyclohexylamide;
4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
4-(4-bromophenyl)-5-phenylthiazole-2-carboxylic acid cyclohexylamide;
4-(4-bromophenyl)-5-phenylthiazole-2-carboxylic acid piperidin-1-ylamide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid cyclohexylamide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
4-(4-methoxyphenyl)-5-phenylthiazole-2-carboxylic acid cyclohexylamide;
4,5-bis-(4-methoxyphenyl)thiazole-2-carboxylic acid cyclohexylamide;
4,5-bis-(4-methoxyphenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
5-(7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-phenylthiazole-2-carboxylic acid piperidin-1-ylamide;

4-(7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-phenylthiazole-2-carboxylic acid piperidin-1-ylamide;

4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-methoxymethylcyclopentyl)-amide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid pyridin-4-ylamide;

4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-ethoxyethyl)amide; and

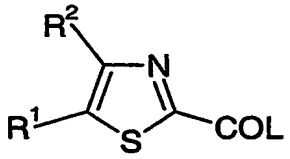
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-morpholin-4-yl-ethyl)amide

and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts and solvates thereof.

Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I in which X is CO may be prepared by reacting a compound of formula III



III

in which R^1, and R^2 are as previously defined and L represents hydroxy, alkoxy or halo (particularly chloro or bromo) with an amine of formula IV

$$R^3H \qquad IV$$

in which R^3 is as previously defined in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide , and optionally in the presence of a catalyst, for example a

basic catalyst, eg 4-dimethylaminopyridine, at a temperature in the range of -25°C to 150°C.

Compounds of formula III may be prepared as described in the Examples and by other methods known to those skilled in the art. Certain compounds of formula II are novel and are claimed as a further aspect of the present invention as useful intermediates.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutically acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with obesity.

A compound of the invention may also be combined with other anti-obesity agents such as Orlistat or a monoamine reuptake inhibitor, for example Sibutramine. Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I (including the compounds of the proviso) in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I including the compounds of the proviso to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). ^{1}H NMR measurements were performed on either a Varian Mercury 300, Varian Unity plus 400 or a Varian INOVA 500, operating at ^{1}H frequencies of 300, 400 and 500 MHz respectively. Chemical shifts are given in ppm with $CDCl_3$ as internal standard if nothing else stated. Purification was performed by semipreparative HPLC if nothing else stated. Two different semipreparative HPLC systems were used:

(a) The Shimadzu system was equipped with a Waters, xTerra 19 x 100 mm C_{18}, 5 µm column and a QP 8000 single quadrupole mass spectrometer. The fraction collector was mass triggered. The mobile phase used was acetonitrile and buffer (0.1 M NH_4OAc:acetonitrile 95:5).

(b) The Waters Prep LC 2000 system was equipped with a HICHROM, 21.1 x 250 mm C_8, 7 μm column. The system was equipped with a UV detector (Waters 2487 Dual λ Absorbance Detector). The mobile phase used was acetonitrile and buffer (0.1 M NH_4OAc:acetonitrile 95:5).

Microwave heating was performed using single node heating in a Smith Creator or Smith Synthesizer from Personal Chemistry, Uppsala, Sweden.

List of Abbreviations

DCM	dichloromethane
t	triplet
s	singlet
d	doublet
q	quartet
m	multiplet
br	broad
dd	doblet of doublet
p	pentet

Synthesis of intermediates

Preparation A

(a) 2-Bromo-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone

Bromine (1 M in acetic acid, 4.66 ml, 4.66 mmol) was added dropwise to 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (1.27 g, 4.23 mmol) dissolved in acetic acid (15 ml) with stirring at room temperature. After stirring at room temperature for 2.5 hours an additional portion of bromine (0.2 eq, 1 M in acetic acid) was added and the mixture was stirred for an additional 3.5 hours. Water (50 ml) was added and the solution was extracted with DCM, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product (1.59 g, 99 %). ^{1}H-NMR (500 MHz) δ 7.49-7.45 (m, 3H), 7.42-7.31 (m, 4H), 6.19 (s,1H). MS *m/z* 375, 377, 379, 381 $(M-H)^-$.

(b) 2-Bromo-2-(7-bromo-2,3-dihydro-benzo[1,4]dioxin-6-yl)-1-phenylethanone

2-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-1-phenylethanone (500 mg, 1.50 mmol) was dissolved in acetic acid (7 ml) and treated with bromine (263 mg, 1.65 mmol) as described in Preparation A step (a). After 5 hours, the reaction mixture was worked up as described in Preparation A step (a) to give the crude product (576 mg, 93 %). MS *m/z* 409, 411, 413 $(M-H)^-$.

Preparation B

Starting materials for Preparation B were either commercially available or described in Preparation A.

(a) 4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester or 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester

Ethyl thiooxamate (75 mg, 0.56 mmol) was added to a solution of 2-bromo-2-(4-chlorophenyl)-1-(2,4-dichloro-phenyl)ethanone (212 mg, 0.56 mmol) from preparation A step (a) in ethanol (10 mL). The mixture was subjected to microwave heating 120 °C for 80 minutes. The solvent was evaporated under reduced pressure and cold acetonitrile was added to the residue. The precipitate was filtered off, the solution concentrated and the residue chromatographed (SiO_2, heptane:ethyl acetate 5:1) to give one of the title compounds (43.5 mg, 19 %). ^{1}H-NMR (400 MHz) δ 7.42 (d, 1H), 7.36 (d, 1H), 7.30-7.26 (m, 3H), 7.16 (m, 2H), 4.50 (q, 2H), 1.45 (t, 3H). MS *m/z* 412, 414, 416 $(M+H)^+$.

(b) 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester or 4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester

Ethyl thiooxamate (76 mg, 0.58 mmol) was added to a solution of 2-bromo-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (220 mg, 0.58 mmol) from preparation A step (a) in ethanol (10 mL). The mixture was subjected to microwave heating at 150 °C for 20 minutes. The solvent was evaporated under reduced pressure, cold acetonitrile was added to the residue. The product precipitated and was filtered off as white solid (53.8 mg, 22 %). ^{1}H-NMR (C_3D_7NO, 400 MHz) δ 8.38 (d, 1H), 7.88 (d, 1H), 7.75-7.67 (m, 3H), 7.64-7.58 (m, 2H), 4.28 (q, 2H), 1.21 (t, 3H). MS *m/z* 412, 414, 416 $(M+H)^+$.

(c) 4-(4-Bromophenyl)-5-phenyl-thiazole-2-carboxylic acid ethyl ester

Ethyl thiooxamate (167 mg, 1.26 mmol) was added to a solution of 2-bromo-1-(4-bromophenyl)-2-phenyl-ethanone (578 mg, 1.16 mmol) in ethanol (25 ml). The mixture was subjected to microwave heating 150 °C for 20 minutes. The solvent was evaporated under reduced pressure, chloroform was added and the precipitate formed was filtered off. The concentrated residue was chromatographed (SiO_2, heptane:ethyl acetate 9:1) to give the title compound (272 mg, 60 %). ^{1}H-NMR (400 MHz) δ 7.48-7.38 (m, 9H), 4.55 (q, 2H), 1.51 (t, 3H). MS *m/z* 389 $(M+H)^+$.

(d) 4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid ethyl ester

Ethyl thiooxamate (203 mg, 1.52 mmol) was added to a solution of 2-bromo-1,2-bis-(4-chlorophenyl)ethanone (525 mg, 1.07 mmol) in ethanol (25 ml). The mixture was subjected to microwave heating at 150 °C for 10 minutes. An additional 0.13 eq. of ethyl thiooxamate was added, and the mixture was heated for another 5 minutes at 150 °C using microwave heating. The solvent was evaporated under reduced pressure, chloroform was added and the precipitate formed was filtered off. The concentrated residue was chromatographed (SiO_2, heptane:ethyl acetate 9:1) to give the title compound (233 mg, 58 %). ^{1}H-NMR (500 MHz) δ 7.48 (m, 2H), 7.39 (m, 2H), 7.34-7.30 (m,4H), 4.54 (q, 2H), 1.49 (t, 3H). MS *m/z* 378, 380, 382 $(M+H)^+$.

(e) 4,5-Bis-(4-methoxyphenyl)thiazole-2-carboxylic acid ethyl ester

Ethyl thiooxamate (195 mg, 1.46 mmol) was added to a solution of 2-bromo-1,2-bis-(4-methoxyphenyl)ethanone (490 mg, 1.46 mmol) in ethanol (25 ml). The mixture was subjected to microwave heating 150 °C for 30 minutes. The solvent was evaporated under reduced pressure. Heptane: ethyl acetate (5:1) was added to the residue and undissolved impurities were filtered off before the residue was concentrated and chromatographed (SiO_2, heptane:ethyl acetate 5:1) to give the impure title compound (317 mg, 52 % purity, 31 %). MS *m/z* 370 $(M+H)^+$. The impure material was taken to the next step without further purification.

(f) 5-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-phenylthiazole-2-carboxylic acid ethyl ester and 4-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-phenylthiazole-2-carboxylic acid ethyl ester

2-Bromo-2-(7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-1-phenylethanone (400 mg, 0.97 mmol) from Preparation A step (b) was treated as described in Preparation B step (a) but heated to 150 °C for 1 hour using microwave heating. Purification by semipreparatory HPLC system (a) gave the two title compounds (30 mg, 6.8 %) and (22 mg, 5.0 %). ^{1}H-NMR (300 MHz) δ 7.30 (s, 5H), 7.08 (s, 1H), 6.93 (s, 1H), 4.50 (q, 2H), 4.26 (q, 4H), 1.45 (t, 3H) and δ 7.76 (s, 1H), 7.57-7.53 (m, 2H), 7.46-7.41 (m, 3H), 7.18 (s, 1H), 4.33-4.26 (m, 6H), 1.24 (t, 3H).

Preparation C

(a) 5-(4-Chloro-phenyl)-4-(2,4-dichlorophenyl)-thiazole-2-carboxylic acid or 4-(4-Chloro-phenyl)-5-(2,4-dichlorophenyl)-thiazole-2-carboxylic acid

Sodium hydroxide (109 mg, 2.73 mmol) was added to a solution of 5-(4-chloro-phenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester or 4-(4-chloro-phenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester (75.0 mg, 0.18 mmol) from preparation B step (b) in ethanol (3 mL). The mixture was refluxed for 2 hours, then allowed to reach room temperature and the solvent was evaporated under reduced pressure. Hydrochloric acid (aq, 2 M, 25 ml) was added and the mixture was stirred overnight. The solution was extracted with ethyl acetate, the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude title compound (68 mg, 97 %). MS *m/z* 384, 386, 388 $(M+H)^+$. The crude product was used in steps described below without further purification.

(b) 4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid ethyl ester (486 mg, 1.28 mmol) from Preparation B step (d) was treated as described in Preparation C step (a) but refluxed for 30 minutes. The reaction mixture was worked up as described in Preparation C step (a) but was not stirred overnight, to give the title compound (434 mg, 97 %) MS *m/z* 350, 352, 354 $(M+H)^+$. The crude product was used without further purification.

Examples of the invention

Example 1

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid cyclohexylamide or 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid cyclohexylamide

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester or 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester (24 mg, 0.058 mmol) from Preparation B step (a) was dissolved in cyclohexylamine (3 mL, 26.2 mmol) and the mixture was subjected to microwave heating at 150 °C for 15 minutes. The solution was evaporated under reduced pressure and the residue was chromatographed (SiO_2, heptane:ethyl acetate 9:1) to give the title compound (24 mg, 82 %). ^{1}H-NMR (400 MHz) δ 7.46 (d, 1H), 7.31-7.24 (m, 3H), 7.15-7.11 (m, 2H), 7.07 (d, 1H), 3.95 (m, 1H), 2.02 (m, 2H), 1.77 (m, 2H), 1.62 (m, 1H), 1.48-1.16 (m, 5H). MS *m/z* 463, 465, 467, 469$(M+H)^+$.

Example 2

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide or 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester or 5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid ethyl ester (42 mg, 0.10 mmol) from Preparation B step (a) was dissolved in *N*-aminopiperidine (3 mL, 27.8 mmol) and the mixture was subjected to microwave heating at 150 °C for 30 minutes. The solution was evaporated under reduced pressure and the residue was chromatographed (SiO_2, toluene:ethyl acetate 1:0 → 5:1) to give the title compound (24 mg, 51 %). ^{1}H-NMR (500 MHz) δ 7.94 (s, 1H), 7.47 (m, 1H), 7.32-7.25 (m, 4H), 7.14 (m, 2H), 2.89 (m, 4H), 1.77 (m, 4H), 1.45 (m, 2H). MS *m/z* 466, 468, 470 $(M+H)^+$.

Example 3

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide or 4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid or 4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid (51 mg, 0.13 mmol) from Preparation C step (a) and 4-dimethylaminopyridine (2 mg, 0.013 mmol) were dissolved in DCM (9 ml) and DMF (0.5 ml). The solution was cooled to 0°C. A slurry of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (32 mg, 0.16 mmol) in DCM (0.5 ml) was added dropwise. After 15 minutes *N*-aminopiperidine (16 μl, 0.15 mmol) in DCM (0.5 ml) was added dropwise. The mixture was allowed to attain room temperature, and was stirred overnight. The mixture was diluted with DCM, washed with $NaHCO_3$ (aq), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, toluene:ethyl acetate 9:1) to give the title compound (20 mg, 31 %). ^{1}H-NMR (500 MHz) δ 8.21 (d, 1H), 7.64 (d, 2H), 7.55 (d, 1H), 7.41 (dd, 1H), 7.38 (d, 2H), 2.96 (br, 4H), 1.77 (br, 4H), 1.46 (br, 2H). MS *m/z* 466, 468, 470 $(M+H)^+$.

Example 4

4-(4-Bromophenyl)-5-phenylthiazole-2-carboxylic acid cyclohexylamide

4-(4-Bromophenyl)-5-phenylthiazole-2-carboxylic acid ethyl ester (52 mg, 0.14 mmol) from Preparation B step (c) was dissolved in cyclohexylamine (2 ml, 17.5 mmol) and the mixture was subjected to microwave heating at 150 °C for 10 minutes. The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, toluene) to give the title compound (40 mg, 68 %). ^{1}H-NMR (400 MHz) δ 7.44 (m, 2H), 7.39-7.31 (m, 7H), 2.04 (m, 2H), 1.78 (m, 2H), 1.66 (m, 1H), 1.49-1.16 (m, 5H). MS *m/z* 441, 443 $(M+H)^+$.

Example 5

4-(4-Bromophenyl)-5-phenylthiazole-2-carboxylic acid piperidin-1-ylamide

4-(4-Bromophenyl)-5-phenylthiazole-2-carboxylic acid ethyl ester (27 mg, 0.070 mmol) from Preparation B step (c) was dissolved in *N*-aminopiperidine (1.5 ml, 13.9 mmol) and the mixture was subjected to microwave heating at 150 °C for 25 minutes. The solution was evaporated under reduced pressure and chromatographed (SiO_2, toluene:ethyl acetate 5:1) to give the title compound (14 mg, 45 %). ^{1}H-NMR (400 MHz) δ 7.99 (s, 1H), 7.44 (m, 2H), 7.39-7.30 (m, 7H), 2.91 (m, 4H), 1.78 (m, 4H), 1.47 (m, 2H). MS *m/z* 442, 444 $(M+H)^+$.

Example 6

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid cyclohexylamide

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid ethyl ester (50 mg, 0.13 mmol) from Preparation B step (d) was dissolved in cyclohexylamine (3 ml, 26.2 mmol) and the mixture was subjected to microwave heating at 180 °C for 30 minutes. The solution was evaporated under reduced pressure and the residue was chromatographed (SiO_2, toluene:ethyl acetate 19:1) to give the title compound (53 mg, 93 %). ^{1}H-NMR (400 MHz) δ 7.42 (m, 2H), 7.35-7.22 (m, 6H), 3.95 (m, 1H), 2.04 (m, 2H), 1.78 (m, 2H), 1.66 (m, 1H), 1.49-1.16 (m, 5H). MS *m/z* 431, 433, 435 $(M+H)^+$.

Example 7

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid ethyl ester (55 mg, 0.14 mmol) from Preparation B step (d) was dissolved in *N*-aminopiperidine (2 ml, 18.5 mmol) and the mixture was subjected to microwave heating at 150 °C for 30 minutes. The solution was evaporated under reduced pressure and the residue was chromatographed (SiO_2, toluene:ethyl acetate 19:1 → 5:1) to give the title compound (26 mg, 41 %). ^{1}H-NMR (400

MHz) δ 7.98 (bs, 1H), 7.41 (m, 2H), 7.36-7.22 (m, 6H), 2.91 (m, 4H), 1.78 (m, 4H), 1.47 (m, 2H). MS *m/z* 432, 434, 436 $(M+H)^+$.

Example 8

4-(4-Methoxyphenyl)-5-phenylthiazole-2-carboxylic acid cyclohexylamide

4-(4-Methoxyphenyl)-5-phenylthiazole-2-carboxylic acid ethyl ester (51 mg, 0.15 mmol) was dissolved in cyclohexylamine (4 ml, 35.0 mmol) and the mixture was subjected to microwave heating at 180 °C for 20 minutes. The solution was evaporated under reduced pressure and the residue was chromatographed twice (SiO_2, toluene: ethyl acetate 19:1 then SiO_2, toluene:ethyl acetate 5:1) to give the title compound (37 mg, 62 %). ^{1}H-NMR (400 MHz) δ 7.43 (m, 2H), 7.34 (m, 4H), 7.18 (m, 1H), 6.84 (m, 2H), 3.96 (m, 1H), 3.82 (s, 3H), 2.03 (m, 2H), 1.78 (m, 2H), 1.66 (m, 1H), 1.49-1.16 (m, 5H). MS *m/z* 393 $(M+H)^+$.

Example 9

4,5-Bis-(4-methoxyphenyl)thiazole-2-carboxylic acid cyclohexylamide

The crude 4,5-bis-(4-methoxyphenyl)thiazole-2-carboxylic acid ethyl ester (54 mg, 0.03 mmol) from Preparation B step (e) was dissolved in cyclohexylamine (3 ml, 26.2 mmol) and the mixture was subjected to microwave heating at 180 °C for 2 hours. The solution was evaporated under reduced pressure and the residue was purified by semipreparative HPLC system (b) to give the title compound (26 mg, 81 %). ^{1}H-NMR (400 MHz) δ 7.44 (m, 2H), 7.27 (m, 2H), 6.88-6.82 (m, 4H), 3.96 (m, 1H), 3.81 (s, 6H), 2.03 (m, 2H), 1.77 (m, 2H), 1.65 (m, 1H), 1.49-1.16 (m, 5H). MS *m/z* 423 $(M+H)^+$.

Example 10

4,5-Bis-(4-methoxyphenyl)thiazole-2-carboxylic acid piperidin-1-ylamide

The crude 4,5-Bis-(4-methoxyphenyl)thiazole-2-carboxylic acid ethyl ester (58 mg, 0.08 mmol) from Preparation B step (e) was dissolved in *N*-aminopiperidine (3 ml, 27.8 mmol) and the mixture was subjected to microwave heating at 150 °C for 3 hours. The solution was evaporated under reduced pressure and the residue was chromatographed (SiO_2,

heptane:ethyl acetate 3:1). The product was not completely pure and another purification by semi-preparative HPLC system (b) gave the title compound (12 mg, 36 %). ^{1}H-NMR (400 MHz) δ 7.43 (m, 2H), 7.26 (m, 2H), 6.88-6.82 (m, 4H), 3.83 (s, 6H), 3.68 (br, 4H), 1.82 (m, 4H), 1.49 (m, 2H). MS *m/z* 424 $(M+H)^+$.

Example 11

5-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-phenylthiazole-2-carboxylic acid piperidin-1-ylamide or 4-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-phenyl-thiazole-2-carboxylic acid piperidin-1-ylamide

5-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-phenythiazole-2-carboxylic acid ethyl ester or 4-(7-Bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-phenyl-thiazole-2-carboxylic acid ethyl ester (29 mg, 0.065 mmol) from Preparation B step (f) was treated and worked-up as described in Example 2. Flash chromatography (SiO_2, hexane:ethyl acetate 2:1) gave the title compound (13 mg, 40 %). ^{1}H-NMR (300 MHz) δ 7.97 (s, 1H), 7.33-7.23 (m, 5H), 7.13 (s, 1H), 6.88 (s, 1H), 4.27 (m, 4H), 2.87 (m, 4H), 1.76 (p, 4H) 1.49-1.38 (m, 2H). MS *m/z* 500, 502 $(M+H)^+$.

Example 12

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-methoxymethylcyclopentyl)amide

The title compound was isolated when 4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid ethyl ester (100 mg, 264 mmol) from Preparation B step (d) was treated with (R)-(+)-2-(methoxymethyl)-1-pyrrolidinamine (2 ml) as described in Example 1 at 180 °C for 15 minutes. Purification by flash chromatography twice (SiO_2, 1 % methanol in DCM then SiO_2, 2.5 % methanol in DCM) gave the title compound (3 mg, 2.5 %). ^{1}H NMR (300 MHz) δ 7.47-7.28 (m, 8H), 4.5 (m, 1H), 4.22 (t, 2H), 3.71 (m, 2H), 3.37 (s, 3H), 2.10-1.91 (m, 4H). MS *m/z* 447, 449, 451 $(M+H)^+$.

Example 13

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid pyridin-4-ylamide

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid (400 mg, 1.14 mmol) from Preparation C step (b) was dissolved in toluene and thionyl chloride (816 mg, 6.86 mmol) was added. The reaction mixture was boiled under reflux for 3 hours. Solvent and excess of thionyl chloride were removed by evaporation under reduced pressure and the residue was dissolved in DCM (16 ml). The solution was divided into eight portions and one of these portions was stirred with 4-aminopyridine (15 mg, 0.16 mmol) and triethylamine (29 mg, 0.29 mmol) at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, toluene then ethyl acetate) to give the title compound (5 mg, 8 %, calculated on 1/8 of the starting material). ^{1}H NMR (500 MHz) δ 9.60 (s, 1H), 8.55 (d, 2H), 7.93 (d, 2H), 7.64 (m, 2H), 7.52 (d, 2H), 7.47 (d, 2H). MS *m/z* 426, 428, 430 $(M+H)^+$.

Example 14

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-ethoxyethyl)amide

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid ethyl ester (110 mg, 0.291 mmol) from Preparation B step (d) was dissolved in 2-ethoxyethylamine (2 ml) and treated as described in Example 1. Chromatography (SiO_2, 1 % methanol in DCM) gave the title compound (77 mg, 63 %). ^{1}H NMR (300 MHz) δ 7.43 (d, 2H), 7.36-7.25 (m, 6H), 3.71-3.60 (m, 4H), 3.55 (q, 2H), 1.24 (t, 3H). MS *m/z* 421, 423, 425 $(M+H)^+$.

Example 15

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-morpholin-4-yl-ethyl)amide

4,5-Bis-(4-chlorophenyl)thiazole-2-carboxylic acid ethyl ester(127 mg, 0.235 mmol) from Preparation B step (d) was dissolved in 2-(4-morpholino)ethylamine (2 ml) and treated as

described in Example 1. Filtration through a Silica plug with methanol as eluent and then flash chromatography (SiO_2, 5 % methanol in DCM) gave the title compound (54 mg, 50 %). ^{1}H NMR (300 MHz) δ 7.43 (d, 2H), 7.38-7.23 (m, 6H), 3.74 (b, 4H), 3.63-3.55 (m, 2H), 2.62 (t, 2H), 2.53 (br, 4H). MS *m/z* 462, 464, 466 $(M+H)^+$.

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

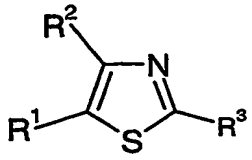
10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [^{35}S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [^{35}S]-GTPγS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar.

Claims

1. A compound of formula (I)



I

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one , two or three groups represented by Z;

Z represents a C_{1-6}alkyl group, a C_{1-6}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl , acetyl or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ; and phenyl optionally substituted by one or more of the following: C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, trifluoromethoxy, or halo or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ;

and

R^3 represents a group –X-Y-NR^4R^5 in which

R^4 and R^5 independently represent :

a C_{1-6}alkyl group optionally substituted by a C_{1-6}alkoxy group or trifluoromethoxy;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

a non-aromatic C_{3-15}carbocyclic group which is optionally substituted by a C_{1-3}alkoxyC_{1-3}alkyl group ;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group –$(CH_2)_r$(phenyl)$_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups or benzyl ;

1-adamantylmethyl;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-6}alkyl group; a C_{1-6}alkoxy group, trifluoromethoxy or halo or Het represents a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

or R^4 represents H and R^5 is as defined above;

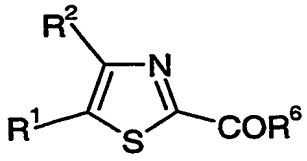
or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

X is CO or SO_2;

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

with the proviso that R^1 and R^2 do not both represent 4-methoxyphenyl and the proviso that when R^1 represents phenyl and R^2 represents phenyl or 4-flouorophenyl, X is CO and Y is absent then the group NR^4R^5 does not represent methyl-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]amino, methylpiperazino, 2-[1-methyl-4-piperidinyl]ethylamino; or [2-[1-(phenylmethyl)-4-piperidinyl]ethyl]amino.

2. A compound of formula I as represented by formula (II)



II

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which

R^1 represents phenyl optionally substituted by one or more of the following: C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, trifluoromethoxy, or halo or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ;

R^2 represents phenyl optionally substituted by one or more of the following: C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, trifluoromethoxy, or halo or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ;

and

R^6 represents 1-piperidinylamino, a C_{3-7}cycloalkylamino group which is optionally substituted by a C_{1-3}alkoxyC_{1-3}alkyl group, pyridylamino wherein the pyridyl ring is optionally substituted by one or more of the following: a C_{1-6}alkyl group; a C_{1-6}alkoxy group or trifluoromethoxy; or R^6 represents a C_{1-6}alkylamino group wherein the alkyl chain is optionally substituted by one or more of the following: a C_{1-6}alkoxy group, trifluoromethoxy or morpholino;

with the proviso that when R^1 represents 4-methoxyphenyl and R^2 represents 4-methoxyphenyl then R^6 does not represent 2-(morpholino)ethyl.

3. A compound selected from:

4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid cyclohexylamide;

5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid cyclohexylamide;

4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;

5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;

5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;

4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;

4-(4-bromophenyl)-5-phenylthiazole-2-carboxylic acid cyclohexylamide;
4-(4-bromophenyl)-5-phenylthiazole-2-carboxylic acid piperidin-1-ylamide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid cyclohexylamide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
4-(4-methoxyphenyl)-5-phenylthiazole-2-carboxylic acid cyclohexylamide;
4,5-bis-(4-methoxyphenyl)thiazole-2-carboxylic acid cyclohexylamide;
4,5-bis-(4-methoxyphenyl)thiazole-2-carboxylic acid piperidin-1-ylamide;
5-(7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-4-phenylthiazole-2-carboxylic acid piperidin-1-ylamide;
4-(7-bromo-2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-phenylthiazole-2-carboxylic acid piperidin-1-ylamide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-methoxymethylcyclopentyl)-amide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid pyridin-4-ylamide;
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-ethoxyethyl)amide; and
4,5-bis-(4-chlorophenyl)thiazole-2-carboxylic acid (2-morpholin-4-yl-ethyl)amide

and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts and solvates thereof.

4. A compound of formula I as claimed in any previous claim for use as a medicament.

5. A pharmaceutical formulation comprising a compound of formula I, as defined in any one of claims 1 to 3 and a pharmaceutically acceptable adjuvant, diluent or carrier.

6. Use of a compound of formula I, as defined in any one of claims 1 to 3 including the compounds of the proviso in claim 1 in the preparation of a medicament for the treatment or prophylaxis of conditions associated with obesity.

7. A method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia,

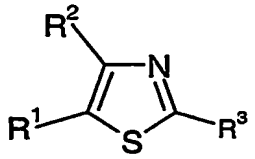
attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 3 including the compounds of the proviso in claim 1 to a patient in need thereof.

8. Processes for the preparation of compounds of formula I as described herein.

9. Intermediates of formula II as described herein.

ABSTRACT

The present invention relates to compounds of formula I



I

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one , two or three groups represented by Z;

Z represents a C_{1-6}alkyl group, a C_{1-6}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl , acetyl or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ; and phenyl optionally substituted by one or more of the following: C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, trifluoromethoxy, or halo or two adjacent carbons may be substituted with the group -O-CH_2-CH_2-O- ;

and

R^3 represents a group –X-Y-NR^4R^5 in which

R^4 and R^5 independently represent :

a C_{1-6}alkyl group optionally substituted by a C_{1-6}alkoxy group or trifluoromethoxy;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

a non-aromatic C_{3-15}carbocyclic group which is optionally substituted by a C_{1-3}alkoxyC_{1-3}alkyl group ;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group –$(CH_2)_r$(phenyl)$_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups or benzyl ;

1-adamantylmethyl;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-6}alkyl group; a C_{1-6}alkoxy group, trifluoromethoxy or halo or Het represents a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

or R^4 represents H and R^5 is as defined above;

or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

X is CO or SO_2;

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

with the proviso that R^1 and R^2 do not both represent 4-methoxyphenyl and the proviso that when R^1 represents phenyl and R^2 represents phenyl or 4-flouorophenyl, X is CO and Y is absent then the group NR^4R^5 does not represent methyl-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]amino, methylpiperazino, 2-[1-methyl-4-piperidinyl]ethylamino; or [2-[1-(phenylmethyl)-4-piperidinyl]ethyl]amino.

processes for preparing such compounds, their use in the treatment of obesity, psychiatric and neurological disorders and to pharmaceutical compositions containing them.